DRAFT

Questions for Discussion

Circulatory System Devices Panel

PRECISE™ (OTW and RX) and ANGIOGUARD™ (OTW and RX) Nitinol Carotid Stent and Emboli Capture Guidewire by Cordis Corp.

P030047

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Evaluation of Clinical Trial Design

The original IDE study design was intended to demonstrate equivalence to CEA (carotid endarterectomy) with a RCT (randomized clinical trial) of 600-900 patients, the ultimate sample to be determined with pre-specified interim analyses. Superiority of CAS (carotid artery stenting) could be claimed with demonstration of a one sided p-value of 0.025.

A decision to terminate the RCT was made after enrolment of 334 patients due, it is claimed, to lack of enrollment. During the study period a concurrent registry enrolled patients who were rejected prior to randomization as unsuitable for CAE or CAS in alternative treatment registries. A total of 406 of 747 patients were entered into the CAS registry arm and 7 CEA registry arm. Of 1153 candidates for randomization, 406 patients were assessed as unsuitable for surgery, and placed into the CAS registry cohort. The reason identified for failure to undergo assigned treatment was explained for 196 of the stent registry subjects, 32% of these because of previous CAE, 13 % following radiation, 10% with a high lesion, and 10% with coronary artery disease.

Single center investigator –sponsored studies were provided access to the sponsor's master file, study template, and the Sapphire follow-up/CRF program. Thirty four sites enrolled 491 patients in so-called feasibility studies and provided additional 30-day safety data. There is no assurance that these patients met the high risk entrance criteria of the pivotal Sapphire study. Additional data was submitted from a European Union (EU) study of 121 patients and from the feasibility study of 261 patients.

The objective of this study was to evaluate CAS for patients at high risk for CEA based on entrance criteria; a largely qualitative designation.

1) **Can the data from the investigator-sponsor studies be considered in the evaluation of high risk carotid stenting given the differences in trial conduct for the high-risk investigator-sponsor registries?**

2) **How does the large enrollment in the registry CAS arm affect interpretation of results?**

3) **How does premature termination of the pivotal randomized study affect conclusions derived from this study?**

Safety and Effectiveness

The Sapphire study primary and secondary endpoints comprise a composite of adverse events occurring at 30 days and between 31 and 360 days, with stroke one component. The secondary endpoints, except for estimation of stroke incidence, are entirely directed towards determining the successful deployment of stent and filter. Historical studies (NASCET, ACAS, ECST) that established the role of CEA did so with randomized trials followed to 2-5 years to determine stroke prophylaxis in "healthy" surgical subjects that included symptomatic and asymptomatic patients and those with stenosis severity up to 90%. Cordis utilized results from the NASCET and ACAS studies to develop their OPC criteria.

The Sapphire **randomized** study reports the following outcomes for the 167 (symptomatic and asymptomatic) patients in each arm:

Adverse Event	30-Day Rates		360-Day Rates	
	CAS	CEA	CAS	CEA
Death	1.2%	2.4%	7.2%	12.6%
Stroke	3.6%	3.0%	6.0%	7.2%
All stroke and death	4.2%	4.8%	5.4%*	7.8%*
Major Ipsilateral stroke	3.0%	1.8%	0.6%	3.0%
Minor Ipsilateral stroke	2.4%	0.6%	3.6%	1.8%
All Ipsilateral stroke	5.4%	2.4%	4.2%	4.8%
TIA	3.6%	2.4%	6.6%	3.0%
TLR	0	0	0.6%	3.6%
MI (Q and non-Q wave)	2.4%	6.0%		

These rates are the MAE exclusive of MI's and non-neurologic deaths

In the randomized cohort, 117 **asymptomatic** patients were randomized to CAS and 120 randomized to CAE with the following outcomes:

Adverse Event	30-Day Rate		360-Day Rate	
	CAS	CEA	CAS	CEA
Death	1.7%	0.8%	5.1%	10.8%
Stroke	5.1%	3.3%	7.7%	7.5%
Ipsilateral Stroke	4.3%	2.5%	5.2%	5.3%
MI (Q and non-Q wave)	2.6%	6.7%	2.6%	8.3%

A **Registry arm** of 406 patients was treated prior to randomization. All but 7 patients were considered at too high a risk for CAE by a surgeon and underwent CEA. One hundred and twenty four patients were symptomatic and 281 asymptomatic. Previous CEA in 38%, high or low lesions in 16%, radiation therapy in 16%, and abnormal stress test were some of the reasons for exclusion of CEA. The outcome in these patients was:

Adverse Event	30-Day Rate		360-Day Rate	
	Overall N=406	Asymptomatic N=281	Overall N=406	Asymptomatic N=281
Death	2.2%	2.8%	10.1%	10.7%
Stroke	4.9%	3.9%	9.1%	8.2%
Ipsilateral Stroke	4.2%	3.2%	7.1%	6.4%
TIA	5.4%	3.2%	6.9%	3.2%
TLR	0.5%	0.4%	0.7%	0.4%
MI (Q and non-Q wave)	1.7%	1.4%	2.7%	2.5%

Factoring in data from the NASCET and ACAS studies, using endpoints as closely matched as possible, the overall data for 30-day and 360-day (unless otherwise noted) are as follows:

30-Day Rates

Event	Symptomatic Patients				Asymptomatic Patients			
	Stent Registry N=124	Stent RCT N=50	CEA RCT N=46	NASCET N=326 with stenosis >70%	Stent registry N=281	Stent RCT N=117	CEA RCT N=120	ACAS* N=825
Major ipsilateral stroke	3.2%	0.0%	0.0%	2.1% disabling	2.1%	0.9%	1.7%	1.2% post angio
Minor ipsilateral stroke	3.2%	0.0%	0.0%	3.7% non-disabling	1.1%	3.4%	0.8%	1.2%
All ipsilateral stroke	6.4%	0.0%	0.0%	5.8%	3.2%	4.3%	2.5%	2.1%
All stroke and death	8.1%	0.0%	6.5%	5.8%	5.0%	6.0%	4.2%	2.3%
death				0%	2.8%	1.7%	0.8%	0.4%

* Ipsilateral strokes were not culled out in the peri-operative period in the ACAS study; these numbers represent all stroke (JAMA, May 10, 1995, Vol. 273, No. 18)

360-Day Rates

Event	Symptomatic Patients				Asymptomatic Patients			
	Stent Registry N=124	Stent RCT N=50	CEA RCT N=46	NASCET 5-Year N=326 with stenosis >70%	Stent registry N=281	Stent RCT N=117	CEA RCT N=120	ACAS N=825 5-year estimates
Major ipsilateral stroke	3.2%	0%	0%	5.1%	3.2%	0.9%	4.2%	6.0% includes deaths
Minor ipsilateral stroke	5.6%	2.0%	0%	7.9%	3.2%	4.3%	2.5%	5.0% includes deaths
All ipsilateral stroke	8.8%	2.0%	0%	13.0%	6.4%	5.2%	5.3%	
MAE (all death and stroke to 30 days, plus ipsilateral stroke >30 days)	16.1%	16.0%	19.6%	31.0% all stroke and death	15.7%	10.3%	19.2%	11.0%
Death	8.9%	12.0%	17.4%		10.7%	5.1%	10.8%	

The AHA recommends that the 30 day mortality rate from all causes for all CEAs should not exceed 2% (AHA 1989 Special Report). Combined morbidity and mortality due to stroke during or after CEA was listed for indication as follows:

Asymptomatic	<3%
TIA	<5%
Stroke	<7%
Recurrent CAE	<10%

The primary effectiveness endpoint for this study was patency (defined as ?50% by ultrasound at 48 hours, 6, 12, 24, and 36 months). To date, information is available out to two years on a subset of the patients enrolled (17.3% restenosis rate in the stent group versus 13.3% in the CEA group).

4) Please discuss how data from previous carotid treatment trials (NASCET, ACAS) can be used to analyze the current peri-operative/30-day data set with regard to safety.

5) There were multiple ways for higher risk patients to be entered into the SAPPHIRE trial. Please discuss the impact of these various patient subgroups on ability to generalize safety and effectiveness results.

6) Effectiveness of stroke prophylaxis has historically required 2 to 5 years monitoring, with safety outcomes generally assessable within the lesser period of 1 year. Please discuss whether chronic data presented in SAPPHIRE trial for the OTW configuration provide evidence of sustained effectiveness of CAS in preventing stroke in patients at high risk for CEA.

7) **Is it appropriate for the sponsor to employ OPCs developed from NASCET and ACAS outcomes to assess outcomes for both symptomatic and asymptomatic patients in the SAPPHIRE Trial? Or should the ACAS rates from the asymptomatic trial be used for comparison?**

8) **The ACAS and NASCET studies did not include myocardial infarction (MI) as an endpoint. The SAPPHIRE trial included MI as a component of MAE. The actual distribution of non-Q-wave MI' s are provided under Tab 8 (Addendum) of the Panel Pack. Please comment on the sponsor's choice of this composite endpoint.**

9) **The indications for carotid artery stenting in the registry arm were largely dictated by hazards of surgical exposure. The ability to deploy a stent should not be affected by these criteria. Are the outcomes achieved in this registry, i.e., 10% stroke and TIA at 30 days and additional 16% at one year acceptable?**

10) **Please comment on whether the incidence of ipsilateral stroke is acceptable.**

11) **The various studies employed a total of only four size 5mm stents. Does the Panel believe that there are adequate safety and effectiveness information for this size?**

12) **Has the totality of data presented for the OTW configuration in the carotid stent PMA shown reasonable assurance of safety and effectiveness? If not, what niche indications have been shown to be safe and effective for carotid stenting?**

Labeling

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the product, and explain how the product should be used to maximize benefits and minimize adverse effects.

The proposed labeling currently contains the following indication statement:

> "The Cordis PRECISE Nitinol Stent System used in conjunction with the ANGIOGUARD XP Emboli Capture Guidewire is indicated for use in the treatment of carotid artery disease in high-risk patients. High-risk is defined as patients with neurological symptoms (one or more TIA's or one or more completed strokes) and ?50% atherosclerotic stenosis of the common or internal carotid artery by ultrasound or angiogram; **OR** patients without neurological symptoms and ?80% atherosclerotic stenosis of the common or internal carotid artery by ultrasound or angiogram. Symptomatic or asymptomatic patients must also have one or more condition(s) that place them at high-risk for carotid endarterectomy."

The proposed labeling currently contains the following contraindications:

"Generally, contraindications to PTA are also contraindicated to stent placement. (note: wording here is awkward and will need to be fixed eventually, but not for the discussion questions since this is the sponsor's current exact wording) They include, but are not limited to:

- ?? Patients with highly calcified lesions resistant to PTA;
- ?? Patients with a target lesion with a large amount of adjacent acute or subacute thrombus;
- ?? Patients with uncorrected bleeding disorders;
- ?? Stenting of intracranial arteries; and
- ?? Patient with chronic total occlusions.

13) Are the indications and contraindications for the OTW configuration clear and supported by the SAPPHIRE study findings? If not, please identify the indication you believe is supported by the sponsor's data. Specifically, is stenting of asymptomatic patients supported? Should any criteria stipulating when stenting of asymptomatic patients is appropriate be included in the labeling?

14) Patients with complex atherosclerotic disease of the aorta or highly tortuous carotid arteries are not optimal candidates for carotid stenting. Please comment on the adequacy of the labeling with regard to patients with these anatomic characteristics. If there are candidates that are not optimal that should be added, please also identify them.

15) Should any other warnings and/or precautions be stipulated in the labeling for the OTW configuration in addition to those found in the proposed labeling?

Post-market Study Design

The sponsor has proposed a post-approval study for a 1000 patient/100 center study conducted by physicians at both academic and private hospitals, who will have a mixture of high, medium and low annual carotid stent implant volumes, geographically distributed. As with the SAPPHIRE study, patients having either *de novo* or restenotic lesions will be consecutively enrolled, under continued access which will then be rolled into a post-approval study, and after consenting. Follow-up will consist of 30-day (primary endpoint) and 9-month assessment of adverse events, plus neurologic examination at discharge and the 30-day period. If ultrasounds are performed as standard of care, they will be collected, but such testing is not a requirement. These events will be adjudicated by a Clinical Events Committee. The stopping rule to be followed will be the two times rule (Goldman formula). The sponsor states that the sample size was chosen because it provides a "high degree of confidence that a rare event will be captured." They then give the example of a sample size of 919, for which the probability of observing at least one event will be 0.99 when the rate of an event is 0.5%.

16) Please comment on whether the sponsor's post approval study plan is adequate. If not, what additional information do you believe should be collected post-approval? Specifically, do you recommend that an independent neurologist make the neurological assessments at each follow-up?

Training

The sponsor has proposed a training program called "CASES" (Carotid Artery Stenting Education System). This program must be completed prior to shipment of any devices to each center. This program will be tailored to the needs of each physician, with more intensive training for those with little or no experience, and less for those already somewhat skilled, as follows:

- Physician with 25 procedures, 10 with Cordis, with acceptable results ? no training
- Physician with 25 cases with acceptable results ? on-line didactic, designated nurse/technician training and a Cordis representative present for first 3 CAS cases
- Other physicians and technicians/nurses ? 5-step training program consisting of:
  - Interactive on-line didactic session (patient criteria, screening and selection, clinical data, device preparation and deployment, device/procedure troubleshooting, and post procedure patient management)
  - Clinical Observation (at "Center of Excellence" for additional didactic and observation of 3 cases with Cordis devices
  - CAS Procedure Simulation Lab (3 CAS procedures on a computer-based program using library of archived procedures. Participant will make equipment, patient management decisions)
  - Staff training/In-Service (nurse(es)/technician(s) will complete on-line didactic and in-service training for patient management, device description and specifications, device preparation and deployment, and device troubleshooting)
  - Proctoring Network (first 3 cases will be proctored)

17) Please comment on whether the sponsor's training plan is adequate. If not, what additional requirements do you believe should be added to the training program?